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10/528,463	03/21/2005	Chantal Guillemette	6013-118US	7564

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,463	GUILLEMETTE, CHANTAL	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8-11,13-15 and 18-31* is/are pending in the application.

4a) Of the above claim(s) *18-29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 8-11, 13-15, and 30* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/14/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 14, 2007. This action is NON FINAL.

Claims 1-2, 8-11, 13-15, and 18-31 and are currently pending. Claims 1, 13, and 31 have been amended. Claims 18-29 and 31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Accordingly Claims 1-2, 8-11, 13-15, and 30 will be discussed herein.

Withdrawn Rejections

2. The rejection made under 35 USC 112 1st paragraph (written description) in section 2 of the Office Action of September 12, 2007 is withdrawn in view of amendments made to the claims.

Claim Objections

The following is a new objection:

3. Claim 1 is objected to because of the following informalities: there appears to be a typo in the phrase "in response to therapy **to** a biologically active compound". This objection could be overcome be amending the claim to recite e.g., "in response to therapy with a biologically active compound". Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a new rejection:

Claims 1-2, 8-11, 13-15, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

The claims are drawn broadly to a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect or a variation in response to therapy with a biologically active compound that is metabolized through UGT1A9 glucuronidation. The claims comprise obtaining a nucleic acid sample from an

individual and determining the presence of a T-275A substitution in the nucleotide sequence of the UGT1A9 gene from the nucleic acid sample of the individual, whereby the presence of the T-275A substitution in the nucleotide sequence is indicative of said predisposition or susceptibility. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Scope of the Claims:

In the instant case the claims are extremely broad for several reasons. First of all the claims are drawn to a method for determining the predisposition or susceptibility of a human individual to an adverse reaction, side effect or a variation in response to therapy. Thus the claims encompass determining a predisposition or susceptibility to any type of adverse reaction (i.e., death, fever, liver failure), any type of side effect (i.e., loss of sleep, anxiety, increased appetite), and any other variation in response to therapy. Additionally the claims are broad because they state that the presence of the T-275A substitution is indicative of the predisposition or susceptibility, however its unknown whether one would have to be homozygous or heterozygous for A at position -275 of the UGT1A9 gene in order to be considered at risk for an adverse reaction, side effect, or variation in response to therapy.

Teachings in the Specification and Examples:

The specification (page 1) teaches that the UDP-glucuronosyltransferase enzymes are a set of enzymes that increase the polarity of xenobiotics, drugs, and

endogenous compounds to facilitate their excretion from the body. Any perturbation in the glucuronidation pathway has the potential to modify the elimination, the detoxification or the pharmacokinetic parameters of a given drug, and consequently drug clearance. Thus human genetic variation leading to differences in the glucuronidation rates could influence the activity of drugs and other chemicals.

Example 3 in specification describes the process in which ten novel polymorphic variations were identified in the UGT1A9 promoter. One of these variations causes a T to A substitution at position -275 of the UGT1A9 gene. In the population that was tested 85% where homozygous for the T allele, 15% were heterozygous for the TA alleles, and 0% were homozygous for the A allele (Table 14).

Example 4 in the specification describes a correlation study that was performed to determine if correlations could exist between the T-275A variation and SN-38, mycophenolic acid, and 4-hydroxyesterone glucuronide formation. The results for this variation are presented in Fig 12. Here you can see a positive correlation between the presence of the -275 mutated allele (A) and higher glucuronidation rate with SN-38. However the specification teaches that the Prob > F value is greater than 0.05, which suggests that these findings were not considered statistically significant.

In the instant case the specification does disclose if any of people who had the T-275A substitution actually had an adverse reaction, side effect or variation in response to treatment with a biologically active compound that is metabolized through UGT1A9 glucuronidation. Without this information it is unclear if the claimed method could actually be used to identify people with a predisposition or susceptibility to an adverse

reaction, side effect, or variation in response to treatment with a biologically active compound that is metabolized through UGT1A9 glucuronidation. Additionally there is no study in the specification which determined the glucuronidation rate of individuals who are homozygous for the A allele at position -275 of the UGT1A9 gene, and this is highly unpredictable.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

It is well known in the art that gene association studies are highly unpredictable. This is demonstrated by Tabor (Nature Reviews Genetics 2002) who teaches that significant findings of association in many candidate gene studies have not been replicated when followed up in subsequent associations studies (Page 1, Column 3). Tabor further indicates that the outcomes of association studies are greatly influenced by the characteristics of the study including the size of the population studied and the number of variables analyzed. Findings of association can be influenced by problems such as selection bias, recall bias, misclassification and confounding. Significant associations might be casual or might simply be the result of coincidence or bias (Page 2, Column 1). Additionally, Lucentini et al (The Scientist 2004) titled his article "Gene Association Studies Typically Wrong" and states that it is strikingly common for follow-up studies to find gene- disease associations wrong (page 2). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (page 2). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the

gene association studies (page 3). This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute 2004) who notes that "too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives" (see abstract). Wacholder further teaches that there is a high chance that an initial statistically significant finding will turn out to be a false positive finding even for large, well designed, and well conducted studies (Page 434 Column 1).

Amount of Direction or Guidance Provided by the Specification:

In the instant case there is no association study between the recited phenotype and genotype described in the specification. This absence is significant in such a highly unpredictable art. The specification teaches that the T–275A substitution of the UGT1A9 gene is associated with higher glucuronidation rates with SN-38, however the Prob > F value is greater than 0.05, which suggests that these findings were not considered statistically significant. Additionally the specification teaches that the presence of this variation can be used to identify humans with a predisposition or susceptibility to an adverse reaction, side effect or a variation in response to therapy, yet the specification does not provide any evidence that individuals with this mutation actually experienced adverse reactions, side effects, or variations in response to therapy. Therefore to determine if an association actually exists between this mutation, higher glucuronidation rates, and a predisposition to an adverse reaction, side effect or variation in response to therapy would require extensive experimentation. For example, such experimentation may involve sequencing the UGT1A9 gene of a large number of individuals who have experienced adverse reactions, side effects, and variations in

response to therapy with a drug that is metabolized through UGT1A9 glucuronidation as well as sequencing the UGT1A9 gene of a large number of individuals who have not experienced adverse reactions, side effects, and variations in response to therapy with a drug that is metabolized through UGT1A9 glucuronidation and identify the frequency of the mutation in both groups. One would also have perform studies aimed at determining the UGT1A9 glucuronidation rates of these individuals. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims are not enabled because the specification does not provide a predictable means for identifying a human individual at risk for adverse

reactions, side effects, and variations in response to therapy with a biologically active compound that is metabolized through UGT1A9 glucuronidation based on the presence of the T-275A substitution of the UGT1A9 gene. In the instant case the claims encompass any type of adverse reaction, any type of side effect, and any other variation in response to therapy, yet the specification does not actually teach anyone with the T-275A substitution that actually experiences these symptoms. Further the claims are not enabled for a method of identifying a human individual with a higher glucuronidation rate based on the presence of the T-275A substitution because the findings present in Table 12 do not appear to be statistically significant. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Arguments

5. In the response filed November 14, 2007, the Applicants amended the claims to overcome the enablement rejection. These amendments have been fully considered; however after further consideration of the specification there still appear to be several enablement issues with the claims. As such a new enablement rejection is set forth above.

Conclusion

6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER